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Novartis drug Afinitor® is first treatment for advanced pancreatic NET to provide overall survival of more than 3.5 years in Phase III trial

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- Afinitor led to an unprecedented median overall survival of 44 months, which represents a clinically meaningful while not statistically significant improvement(1)
- Pancreatic NET (pNET) affects about 2.2 per 1 million people worldwide annually; the advanced form is aggressive and has limited treatment options(2,3)
- Results affirm the role of mTOR (mammalian target of rapamycin) inhibition in advanced pNET; data to be submitted to health authorities(1,4)

EAST HANOVER, N.J., Sept. 27, 2014 /PRNewswire/ -- Novartis today presented final results on overall survival (OS) from a Phase III trial of Afinitor® (everolimus) tablets plus best supportive care (BSC) compared to placebo plus BSC in patients with well-differentiated advanced and progressive pancreatic neuroendocrine tumors (pNET)[1]. Overall survival was a secondary endpoint of the trial[1]. The findings were presented at the European Society for Medical Oncology (ESMO) Congress, September 26-30, 2014 in Madrid, Spain, and are to be submitted to health authorities for inclusion in the Afinitor prescribing information.

Results from the RADIANT-3 trial showed a median OS of 44.02 months (95% confidence interval [CI]: 35.61, 51.75) in the everolimus treatment arm and 37.68 months (95% CI: 29.14, 45.77) in the placebo arm[1]. The 6.34 month difference between the two arms was not statistically significant (Hazard Ratio [HR] 0.94; 95% CI: 0.73, 1.20; p=0.300)[1]. A high crossover of patients from placebo to everolimus (85%) likely contributed to the long median OS in the placebo arm of 37.68 months and may have confounded the ability to detect a difference in the OS results[1].

"The median overall survival of 44 months for everolimus is unprecedented in controlled clinical trials for advanced progressive pancreatic neuroendocrine tumors," said James Yao*, MD, lead investigator, The University of Texas MD Anderson Cancer Center, Houston, Texas. "The results affirm the importance of targeting key pathways involved in tumor growth, such as the mTOR pathway in advanced pNET."

The safety profile was consistent with that observed for everolimus in advanced pancreatic NET and no unexpected or new safety concerns were identified at the time of this analysis, indicating that longer term treatment with everolimus continues to provide a positive benefit-risk ratio for patients[1]. The most commonly reported (≥40%) adverse events (AEs) for everolimus compared to placebo during the core phase of the study were stomatitis (53.9% vs. 13.3%), rash (52.5% vs. 15.8%), diarrhea (48.0% vs. 23.6%) and fatigue (44.6% vs. 26.6%)[1]. The most common (≥40%) AEs reported with everolimus during this follow-up phase were stomatitis (46.7%), diarrhea (43.6%) and rash (40.0%)[1].

Pancreatic NET originates from the islet cells of the pancreas and can grow aggressively[2]. It is uncommon and distinct from what is generally referred to as pancreatic cancer or pancreatic exocrine cancer[5]. The majority of patients with pNET have advanced disease at the time of diagnosis, meaning the cancer has spread to other

parts of the body and has become more difficult to treat[2,3].

"Novartis has more than 25 years of helping to advance NET care and this study, part of the largest global clinical program in NET, emphasizes our commitment to helping fulfill unmet needs for patients living with this disease," said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. "We are pleased to see that Afinitor provided more than 3.5 years of overall survival in patients with progressive, well-differentiated pNET, an advanced and aggressive cancer."

The presentation at ESMO 2014 is an analysis of the mature OS results. Results from the primary analysis, which focused on the progression-free survival (PFS) endpoint in which Afinitor more than doubled median PFS vs. placebo, were previously published in the New England Journal of Medicine (NEJM; February 2011).

About the study

RADIANT-3 (RAD001 In Advanced Neuroendocrine Tumors) is a Phase III prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter study[1]. The core phase of the trial examined the efficacy and safety of everolimus plus BSC versus placebo plus BSC in 410 patients with advanced, low- or intermediate-grade pancreatic NET, also known as islet cell tumors[1]. Patients who met the study entry criteria were randomized 1:1 to receive either everolimus 10 mg once-daily (n=207) or daily placebo (n=203) orally, both in conjunction with BSC[1]. The primary endpoint was PFS, and the key secondary endpoints were OS and the safety and tolerability of everolimus[1].

Patients on placebo whose disease progressed during the core phase were allowed to cross over to open-label everolimus. In addition, when all patients were unblinded at the end of the core phase, those initially assigned to placebo were offered to switch to open-label everolimus and those in the everolimus arm could transition to open-label everolimus[1]. During the open-label phase patients continued with treatment until disease progression was documented by the investigator[1]. At this point, patients discontinued the study drug and entered the follow-up period to be monitored monthly for survival information[1]. All patients initially randomized to placebo were included in the placebo arm results, even if they crossed over to everolimus therapy after progression or unblinding[1]. In total, 85% of patients in the placebo arm crossed over to everolimus during the course of the study[1].

In the double-blind phase, serious adverse events (SAEs) were reported more often in the everolimus arm than in the placebo arm (41.2% vs. 25.6%)[4]. The most commonly reported SAEs (≥2% incidence) in the everolimus arm were pyrexia (3.9%), pneumonitis (3.4%), anemia (3.4%), abdominal pain (2.9%), dyspnea (2.9%), diarrhea (2.5%), pulmonary embolism (2.5%), asthenia (2.5%) and dehydration (2.5%)[4]. The frequency of AEs leading to study drug discontinuation during the double-blind period was higher for the everolimus treatment group (21.1%) compared to the placebo group (5.9%)[4]. In the open-label period, 23.6% of patients discontinued treatment due to AEs[4].

At the time of the final OS analysis there were 126 (60.9%) deaths in the everolimus arm and 130 (64.0%) deaths in the placebo arm[1]. While no statistically significant difference was evident in terms of OS, the median OS favored the everolimus arm, with a clinically meaningful improvement of 6.34 months over placebo, and supports the concept of starting treatment with everolimus early, once progression is detected[1]. The OS benefit is consistent with the statistically significant gain of 6.44 months in PFS (HR 0.35; 95% CI: 0.27-0.45; $p<0.001$) observed in the primary analysis[1,6].

About Afinitor® (everolimus) tablets

Afinitor® (everolimus) is approved in more than 85 countries including the United States and European Union for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin. It is also approved in more than 100 countries, including the United States and throughout the European Union, for advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy.

Afinitor (everolimus) is approved in the European Union for the treatment of hormone receptor-positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI). In the United States, Afinitor is approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative (advanced HR+/HER2-) breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

Everolimus is also available from Novartis for use in certain non-oncology patient populations under the brand names Afinitor® or Votubia®, Certican® and Zortress® and is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Indications vary by country and not all indications are available in every country. The safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

Important Safety Information about Afinitor (everolimus) tablets

Afinitor/Votubia can cause serious side effects including lung or breathing problems, infections (including sepsis), and kidney failure, which can lead to death. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors may be at an increased risk for angioedema. Mouth ulcers and mouth sores are common side effects. Afinitor/Votubia can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and triglyceride levels. Afinitor/Votubia may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of child-bearing potential while receiving Afinitor/Votubia and for up to eight weeks after ending treatment. Women taking Afinitor/Votubia should not breast feed. Fertility in women and men may be affected by treatment with Afinitor/Votubia.

The most common adverse drug reactions (incidence ≥10 percent) are mouth ulcers, skin rash, feeling tired or weak, diarrhea, absence of menstrual periods, infections (including upper respiratory tract infection, sore throat and runny nose, sinusitis, and pneumonia), nausea, decreased appetite, low level of red blood cells, high levels of cholesterol, abnormal taste, acne, irregular menstrual periods, inflammation of lung tissue, high level of blood sugar, weight loss, itching, swelling of extremities or other parts of the body, nose bleeds, and headache. The most common Grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers, absence of menstrual periods, low level of red blood cells, infections (including pneumonia), high level of blood sugar, feeling tired or weak, low white blood cells, inflammation of lung tissue, diarrhea, and spontaneous bleeding or bruising. Cases of hepatitis B reactivation, blood clots in the lung or legs, and pneumocystis jirovecii pneumonia (PJP) have been reported. Abnormalities were observed in hematology and clinical chemistry laboratory tests.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "to be submitted," "indicating," "continues," "commitment," "concept," "has not yet," "will," or similar terms, or by express or implied discussions regarding potential new marketing approvals, indications or labeling for

everolimus, or regarding potential future revenues from everolimus. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that everolimus will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that everolimus will be commercially successful in the future. In particular, management's expectations regarding everolimus could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets innovative medicines aimed at improving patients' lives. We offer a broad range of medicines for cancer, cardiovascular disease, endocrine disease, inflammatory disease, infectious disease, neurological disease, organ transplantation, psychiatric disease, respiratory disease and skin conditions. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 135,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit http://www.novartis.com.

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* Dr. Yao has served as a consultant and has received research funding from Novartis

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